



Clinical trial results:

A multicenter, open-label, single-arm study of the safety and antitumoral efficacy of nivolumab in combination with selective internal radiation therapy (SIRT) using SIR-Spheres for the treatment of patients with hepatocellular carcinoma that are candidates for locoregional therapies.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-000232-34 |
| Trial protocol | ES |
| Global end of trial date | 30 April 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 06 February 2022 |
| First version publication date | 06 February 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | NASIR-HCC |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03380130 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | BMS protocol code: CA209-992 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Clínica Universidad de Navarra/Universidad de Navarra |
| Sponsor organisation address | Avenida Pío XII, 36, Pamplona, Spain, 31008 |
| Public contact | UCEC, Clinica Universidad de Navarra, 34 948255400, ucicec@unav.es |
| Scientific contact | UCEC, Clinica Universidad de Navarra, 34 948255400, ucicec@unav.es |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 April 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of nivolumab in combination with SIRT using SIR-Spheres.

The secondary objective is to evaluate the antitumoral activity of nivolumab in combination with SIRT using SIR-Spheres.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 18 October 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 42 |
| Worldwide total number of subjects | 42 |
| EEA total number of subjects | 42 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 20 |
| From 65 to 84 years | 22 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Child Pugh A subjects with intermediate or advanced hepatocellular carcinoma who are candidates to locoregional therapies but not good candidates to TACE were recruited.

Pre-assignment

Screening details:

40 patients were planned. 53 patients were screened, there were 11 screening failures and 42 patients received SIRT and are included in the safety analysis, while 41 received at least one dose of nivolumab and are included in the efficacy analysis. 14 patients completed the study as planned.

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Treatment period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|--------------------|
| Arm title | Experimental group |
|-----------|--------------------|

Arm description:

Nivolumab in combination with SIR-Spheres Y90 resin microspheres. Patients were treated with SIR-Spheres followed 3 weeks later by nivolumab every 2 weeks for up to 24 doses or until discontinuation based on protocol instructions.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Nivolumab was administered IV starting 3 weeks after SIRT at a dose of 240 mg IV over 30 minutes every 2 weeks for up to 24 doses unless tumor progression, unacceptable toxicity or death.

| | |
|--|--------------|
| Investigational medicinal product name | SIR-Spheres |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Implant |
| Routes of administration | Implantation |

Dosage and administration details:

SIR-Spheres Y90 resin microspheres was the non-investigational product. Y90 activity was calculated according to targeted liver volume and status of cirrhosis. SIRT evaluation and treatment were performed as a single-day procedure at Clínica Universidad de Navarra.

| | |
|---------------------------------------|--------------------|
| Number of subjects in period 1 | Experimental group |
| Started | 42 |
| Completed | 14 |
| Not completed | 28 |
| Physician decision | 4 |
| Disease progression | 17 |

| | |
|--------------------------|---|
| Adverse event, non-fatal | 7 |
|--------------------------|---|

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values | Treatment period | Total | |
|---|------------------|-------|--|
| Number of subjects | 42 | 42 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 20 | 20 | |
| From 65-84 years | 22 | 22 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 65 | | |
| inter-quartile range (Q1-Q3) | 49 to 79 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 6 | 6 | |
| Male | 36 | 36 | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Experimental group |
| Reporting group description: Nivolumab in combination with SIR-Spheres Y90 resin microspheres. Patients were treated with SIR-Spheres followed 3 weeks later by nivolumab every 2 weeks for up to 24 doses or until discontinuation based on protocol instructions. | |

Primary: Safety

| | |
|--|-----------------------|
| End point title | Safety ^[1] |
| End point description: The primary endpoints were the rate and type of adverse events (AEs), serious AEs (SAEs), events of liver decompensation, and transient and permanent drug discontinuations due to toxicity. | |
| End point type | Primary |
| End point timeframe: | |
| End of follow up | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety was the primary endpoint. Results are shown in the corresponding section.

| | | | | |
|-----------------------------|--------------------|--|--|--|
| End point values | Experimental group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 42 | | | |
| Units: Safety | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

| | |
|------------------------|-------------------------|
| End point title | Objective response rate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| End of follow up | |

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Experimental group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 41.5 (26.3 to 57.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

| | |
|------------------------|----------------------|
| End point title | Disease control rate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| End of follow up | |

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Experimental group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 92.7 (80.1 to 98.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

| | |
|------------------------|---------------------|
| End point title | Time to progression |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| End of follow up | |

| | | | | |
|---------------------------------------|--------------------|--|--|--|
| End point values | Experimental group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 8.8 (7.0 to 10.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

| | |
|------------------------|---------------------------|
| End point title | Progression-free survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| End of follow up | |

| | | | | |
|---------------------------------------|--------------------|--|--|--|
| End point values | Experimental group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 9.0 (7.0 to 10.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|------------------------|------------------|
| End point title | Overall survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| End of follow up | |

| | | | | |
|---------------------------------------|---------------------|--|--|--|
| End point values | Experimental group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 20.9 (17.7 to 24.1) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed continuously during the study and for 100 days post last treatment and evaluated according to the NCI CTCAE Version 4.03 dated 14-Jun-2010.

Adverse event reporting additional description:

Additional information: 2 SAEs in the same subject (Pyrexia and Liver abscess) were related to SIRT.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | ND |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Experimental group |
|-----------------------|--------------------|

Reporting group description: -

| Serious adverse events | Experimental group | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 42 (50.00%) | | |
| number of deaths (all causes) | 27 | | |
| number of deaths resulting from adverse events | 6 | | |
| Vascular disorders | | | |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Performance status decreased | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoperitoneum | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Anal abscess | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridium bacteraemia | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Liver abscess | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis bacterial | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Postoperative wound infection | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Experimental group | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 42 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Skin ulcer | | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 42 (2.38%)</p> <p>1</p> <p>1 / 42 (2.38%)</p> <p>1</p> | | |
| <p>Surgical and medical procedures</p> <p>Radiotherapy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 42 (2.38%)</p> <p>2</p> | | |
| <p>General disorders and administration site conditions</p> <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oedema peripheral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oedema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>9 / 42 (21.43%)</p> <p>9</p> <p>7 / 42 (16.67%)</p> <p>8</p> <p>3 / 42 (7.14%)</p> <p>3</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>1 / 42 (2.38%)</p> <p>1</p> <p>1 / 42 (2.38%)</p> <p>1</p> | | |
| <p>Immune system disorders</p> <p>Contrast media allergy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 42 (2.38%)</p> <p>1</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Bronchospasm</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 42 (7.14%)</p> <p>4</p> | | |

| | | | |
|--|------------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | | |
| Asthmatic attack subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 11 / 42 (26.19%) 18 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 14 / 42 (33.33%) 17 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 9 / 42 (21.43%) 12 | | |
| Blood creatine increased subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 3 | | |
| Amylase increased subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | | |
| Gamma-glutamyltransferase | | | |

| | | | |
|--|----------------|--|--|
| increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 2 | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 4 | | |
| Dizziness | | | |

| | | | |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 13 / 42 (30.95%) | | |
| occurrences (all) | 16 | | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 6 | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | | |
| occurrences (all) | 5 | | |
| Eosinophilia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Monocytosis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | | |
| occurrences (all) | 10 | | |
| Diarrhoea | | | |

| | | | |
|---------------------------------|-----------------|--|--|
| subjects affected / exposed | 8 / 42 (19.05%) | | |
| occurrences (all) | 8 | | |
| Nausea | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | | |
| occurrences (all) | 7 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 4 | | |
| Ascites | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 4 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 2 | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Chronic gastritis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Epigastric discomfort | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------------|--|--|
| Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 11 | | |
| Hypertransaminasaemia subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | | |
| Autoimmune hepatitis subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 2 | | |
| Hepatic function abnormal subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Liver abscess subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Portal vein thrombosis subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 8 | | |
| Rash subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 4 | | |
| Dermatitis subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | | |
| Skin lesion subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Skin ulcer subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Renal and urinary disorders | | | |

| | | | |
|--|------------------------|--|--|
| Renal impairment subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | | |
| Dysuria subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Haematuria subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Nephritis subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 5 | | |
| Thyroiditis subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 13 / 42 (30.95%) 13 | | |
| Arthritis subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Muscular weakness subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Musculoskeletal pain | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Soft tissue mass | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | | |
| occurrences (all) | 8 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 2 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 2 | | |
| Tooth infection | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences (all) | 2 | | |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---------------------|--|--|
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Peritonitis bacterial subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Pneumonia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | | |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | | |
| Gout subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Type 2 diabetes mellitus subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Underweight subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | | |
| Vitamin D deficiency | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 25 September 2017 | Addition of Hospital de Cruces as a new study site (no. 09). Approved by the IEC/REC on 13/October/2017 and notified to AEMPS on 17/October/2017 |
| 10 January 2018 | Substantial modifications and updates to IB version 16, ICF/PIS version 3.0 and protocol version 3.0 (Addition of the EQ5-CD questionnaire, minimal change of the SIR-Spheres Activity calculation method and addition of an ICF/PIS for post-progression treatment). Approved by the IEC/REC on 12/February/2018 and by AEMPS on 15/February/2018 |
| 03 September 2018 | Substantial modification to IB version 17 (update of the reference safety information), ICF/PIS version 4.0 (updated with the new European data protection regulation). Approved by the IEC/REC on 01/October/2018 and by AEMPS on 19/October/2018 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

It was determined that the reported protocol deviations had no impact on the interpretability of the study results. The major deviations were notified to the corresponding authorities and a root cause analysis was carried out in each case.

Notes: